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EXAMINER	
BLUMEL, BENJAMIN P	
ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
09/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/540,843	MARISCAL-GONZALEZ ET AL.	
	Examiner	Art Unit	
	BENJAMIN P. BLUMEL	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/14/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-31,42 and 45* is/are pending in the application.

4a) Of the above claim(s) *10-15, 17-21 and 24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9,16,22,23,31 and 43* is/are rejected.

7)☒ Claim(s) *45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/27/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants are informed that the rejections of the previous Office action not stated below have been withdrawn from consideration in view of the Applicant's arguments and/or amendments.

Election/Restrictions

This application contains claims 10-15, 17-21 and 24-30 are drawn to species nonelected without traverse in the reply filed on 10/7/08. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 8, 9, 16, 22, 23, 31, 43 and 45 are examined on the merits. Claim 45 is new and claim 8 has been amended to include newly submitted limitations.

Response to Arguments

Applicant's arguments with respect to claims 8, 9, 16, 22, 23 and 43 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(New Rejection Necessitated by Amendments) Claims 8, 9, 16, 22 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Langridge and Arakawa (US PGPub 2002/0055618 A1) and Potter et al. (US Pat. 5,422,110).

The claimed invention is drawn to a pharmaceutical composition for the delivery of a therapeutic agent that comprises the agent and an effective amount of a VP8 rotavirus protein or derived peptide thereof or a fusion protein comprising the VP8 protein or a peptide derived from the VP8 protein. The therapeutic agent can be a peptide with biological activity and the composition is formulated for oral administration and contains a pharmaceutically acceptable vehicle. The biologically active peptide can be a hormone (i.e., therapeutic agent).

Langridge and Arakawa teach the formation of various fusion proteins that can contain different autoimmune autoantigens or pathogen autoantigens. Some examples are cholera toxin subunits, human insulin, rotavirus VP4, VP6, and shiga toxin. One specific example is the fusion of insulin to a cholera toxin subunit. Langridge and Arakawa teach that by administering such a fusion protein to a host, the onset of insulin-dependent diabetes mellitus (IDDM) can be mitigated. Langridge and Arakawa also teach that for oral administration, tablets can be used. However, Langridge and Arakawa do not specifically state that any pathogen autoantigen (i.e., rotavirus VP8) should be associated/linked to a hormone thereby enhancing the transmission of a therapeutic agent to the epithelia or endothelia. *See paragraphs 190 and 226-228 and example 1.*

Potter et al. teach the creation of a fusion protein based on the bacterial protein *leukotoxin* (a peptide with biological activity) and either somatostatin (SRIF), gonadotropin releasing hormone (GnRH) or rotavirus viral protein 4 (VP4). These fusion proteins are created through recombinant DNA techniques and are formulated for various routes of administration (i.e., oral, nasal, etc.) Moreover, for oral administrations, Potter et al. suggest using tablets, pills, and

capsule, which would function as a pharmaceutically acceptable vehicle. However, they do not teach the use rotavirus VP8 protein or a derivative thereof in delivery of a therapeutic agent to a cell. *See columns 2 (lines 37-62), 14-15 (abridging paragraph) and example 2.*

Tihova et al. teach the analysis of rotavirus VP8 and VP5 (subunits of VP4) with regard to antibody neutralization. Tihova et al. teach that rotavirus containing intact VP4 proteins are capable of infecting the epithelia of the small intestine. However, when VP4 is cleaved by trypsin, which results in the generation of subunits VP8 and VP5, rotavirus infectivity is markedly increased. From this, Tihova et al. proposed that VP8 and VP5 bind to the cellular surface and mediate cell entry via sialic acid molecules and integrin motifs, respectively. *See abstract and page 986.*

It would have been obvious to one of ordinary skill in the art to modify the compositions taught by Langridge and Arakawa in order to use the rotavirus VP8 protein fused to a therapeutic agent (i.e., hormone) as a means of delivering the insulin to the target cell via the oral route. One would have been motivated to do so, given the suggestion by Langridge and Arakawa that fusion proteins based on a protein from a pathogen, such as rotavirus VP4, and a therapeutic gene, such as hormone, can be generated and formulated for oral administration. There would have been a reasonable expectation of success, given the knowledge that rotavirus VP4 (which contains VP8) or fragments thereof can be used in making a fusion protein with biological activity *in vivo*, as taught by Potter et al., and also given the knowledge that rotavirus VP8 and VP5 target specific extracellular molecules during the viral infection cycle, as taught by Tihova et al. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to arguments:

Applicants argue that none of the cited references in the previous Office action teach the use of a rotavirus VP8 protein or derivative thereof that mediates the transfer of a therapeutic agent through epithelia or endothelia. Moreover, Potter et al. teach the use of a domain of the rotavirus VP4 protein (of which VP8 is a derivative of) that VP8 does not contain. Applicants also state that they have determined that domains present on the rotavirus VP8 protein resemble the extracellular loops of the tight junction (TJ) proteins on the extracellular surface of cells. More specifically, these TJ proteins are occludin and claudin. Therefore, based on the prior art of record, a skilled artisan would not have a reason for using VP8 or a peptide derived thereof for enhancing the passage of a therapeutic agent through epithelia or endothelia.

In response, it is acknowledged that none of the previously cited references teach the use of rotavirus VP8 or a fusion protein containing VP8 or a derivative thereof to deliver a therapeutic agent through endothelia or epithelia. However, Potter et al. teach that VP4 or fragments thereof (see Example 2) can be used in generating a fusion protein for *in vivo* applications. Therefore, one fusion protein option taught by Potter et al. would contain the VP8 protein along with the remainder of the VP4 specific sequences if full-length VP4 was employed in the fusion protein. From these teachings of Potter et al. and Langridge/Arakawa in view of Tihova et al., one of ordinary skill in the art would have a reasonable expectation of success at generating a composition containing the VP8 protein and a therapeutic agent for delivery of the agent to the epithelia or endothelia and subsequent passage of the agent through the epithelia or endothelia. The achievement of delivery of the agent is due to the recognized involvement

(Tihova et al.) of rotavirus VP8 in the targeting of extracellular molecules during viral entry of the target cell.

Further in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., targeting of Tight Junctions/occludens and claudins by the VP8 in order to enhance the passage of a therapeutic agent through epithelia and endothelia) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

(New Rejection Necessitated by Amendments) Claims 23 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Langridge and Arakawa (*supra*), Potter et al. (*supra*), and Tihova et al. (*supra*) as applied to claims 8, 9, 16, 22 and 43 above, and further in view of Honeyman et al. (Diabetes, 2000).

The claimed invention also requires that the therapeutic agent by insulin.

However, Langridge/Arakawa, Potter et al. and Tihova et al. do not specifically state that any pathogen autoantigen (i.e., rotavirus VP8) should be associated/linked to insulin thereby enhancing the transmission of a therapeutic agent to the epithelia or endothelia.

Honeyman et al. teach that in some instances, children infected by rotaviruses can develop type 1 diabetes and therefore require insulin supplementations over time. More specifically, Honeyman et al. report that rotaviruses contain certain epitopes that mimic that of the T-cell specific epitopes to self-antigens on the surface of Pancreatic Islet cells. Therefore,

following exposure to rotaviruses, it is possible that circulating T-cells can then mistakenly target these islet cells. *See page 1319.*

It would have been obvious to one of ordinary skill in the art to modify the compositions taught by Langridge and Arakawa in order to use the rotavirus VP8 protein fused to insulin as a means of delivering the insulin to the target cell via the oral route. One would have been motivated to do so, given the suggestion by Langridge and Arakawa that fusion proteins based on a protein from a pathogen, such as rotavirus VP4, and a therapeutic gene, such as insulin, can be generated and formulated for oral administration. There would have been a reasonable expectation of success, given the knowledge that rotavirus VP4 (which contains VP8) or fragments thereof can be used in making a fusion protein with biological activity *in vivo*, as taught by Potter et al., also given the knowledge that rotavirus VP8 and VP5 target specific extracellular molecules during the viral infection cycle, as taught by Tihova et al., and also given the knowledge that in certain documented rotavirus infections, IDDM onset is associated, as taught by Honeyman et al. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to arguments:

Applicants also argue that since Honeyman et al. teach an association between rotavirus infections in children and an increased risk for developing Type 1 Diabetes, a skilled artisan would have avoided the use of a rotavirus protein since this may exacerbate or induce Type 1 Diabetes.

In response, Honeyman et al. (page 1319, right hand column) stated that rotavirus VP7, not VP4 or VP8 contain the T-Cell specific epitopes that mimic self-antigens presented by Pancreatic Islet cells. Therefore, one of ordinary skill in the art would avoid using VP8 in order to deliver insulin to tissues or through epithelia or endothelia.

Claim Objections

Claim 45 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed. SEQ ID NO:s 3 and 7 are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN P. BLUMEL whose telephone number is (571)272-4960. The examiner can normally be reached on M-F, 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachariah Lucas/
Supervisory Patent Examiner, Art Unit 1648

/BENJAMIN P BLUMEL/
Examiner
Art Unit 1648